



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-D-3130]

Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device

Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions; Guidance for Industry and Food and Drug Administration Staff; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a final guidance entitled "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions." This guidance document describes FDA's current approach to considering uncertainty in making benefit-risk determinations to support certain FDA premarket decisions for medical devices--premarket approval applications (PMAs), De Novo requests, and humanitarian device exemption applications. This guidance document elaborates on the consideration of uncertainty as part of our overarching approach to a benefit-risk based framework that is intended to assure greater predictability, consistency, and efficiency through the application of least burdensome principles. This guidance also provides examples of how the principles for considering uncertainty could be applied in the context of clinical evidence and circumstances where greater uncertainty could be appropriate in premarket decisions, balanced by postmarket controls--PMAs for Breakthrough Devices and PMAs for devices for small patient populations.

DATES: The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit either electronic or written comments on Agency guidances at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2018-D-3130 for "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions; Guidance for Industry and Food and Drug Administration Staff; Availability." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made

publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential."

Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

An electronic copy of the guidance document is available for download from the internet. See the SUPPLEMENTARY INFORMATION section for information on electronic access to the guidance. Submit written requests for a single hard copy of the guidance document entitled "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions" to the Office of Policy, Guidance and Policy Development, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 5431, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your request.

FOR FURTHER INFORMATION CONTACT: Sonja Fulmer, Office of Policy, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 5451, Silver Spring, MD 20993-0002, 240-402-5979.

SUPPLEMENTARY INFORMATION:

I. Background

The 1976 Medical Device Amendments (Pub. L. 94-295) to the Federal Food, Drug, and Cosmetic Act (FD&C Act) established a risk-based framework for the regulation of medical devices. The law established a three-tiered risk classification system based on the risk posed to patients should the device fail to perform as intended. Under this system, devices that pose greater risks to patients are subject to more regulatory controls and requirements. Generally, for any regulatory decision, there exists some uncertainty around benefits and risks. The Agency generally provides marketing authorization for a device when it meets the applicable standards, including that its benefits outweigh its risks.

In 2015, following pilots conducted over 4 years, FDA established the Expedited Access Pathway (EAP) Program as a voluntary program for certain medical devices that address an unmet need in the treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. Under this program, an eligible device subject to a PMA could be approved with greater uncertainty about the product's benefits and risks, provided that, among other requirements, the data still support a reasonable assurance of safety and effectiveness, including that the probable benefits of the device outweigh its risks for a patient population with unmet medical needs. For devices subject to PMA, the Agency has the authority to impose, when warranted, postmarket requirements, including post-approval studies and postmarket

surveillance, as a condition of approval, which could be used to address this greater uncertainty.¹

In the Breakthrough Device provisions of the FD&C Act, as added by the 21st Century Cures Act (Cures Act) and amended by the FDA Reauthorization Act of 2017 (FDARA), Congress codified and expanded this program to include devices reviewed through a 510(k) notification.²

This guidance provides further information on how FDA considers uncertainty in benefit-risk determinations for PMAs, De Novo requests, and Humanitarian Device Exemption applications. FDA considered comments received on the draft guidance that appeared in the *Federal Register* of September 6, 2018 (83 FR 45247). FDA revised the guidance as appropriate in response to the comments.

II. Significance of Guidance

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. This guidance is not subject to Executive Order 12866.

III. Electronic Access

Persons interested in obtaining a copy of the guidance may do so by downloading an electronic copy from the internet. A search capability for all Center for Devices and Radiological Health guidance documents is available at

¹ See sections 513(a)(3)(C), 515(c)(5)(C), 515(d)(1)(B)(ii), and 515B(e)(2)(C) of the FD&C Act (21 U.S.C. 360c(a)(3)(C), 360e(c)(5)(C), 360e(d)(1)(B)(ii), and 360e-3(e)(2)(C)); 21 CFR 814.82.

² See section 515B of the FD&C Act, as created by section 3051 of the Cures Act (Pub. L. 114-255) and amended by section 901 of FDARA (Pub. L. 115-52).

<https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm>. This guidance document is also available at <https://www.regulations.gov> or <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>. Persons unable to download an electronic copy of "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions" may send an email request to CDRH-Guidance@fda.hhs.gov to receive an electronic copy of the document. Please use the document number 17039 to identify the guidance you are requesting.

IV. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in the following FDA regulations and guidance have been approved by OMB as listed in the following table:

21 CFR Part; Guidance; or FDA Form	Topic	OMB Control No.
814, subparts A through E	Premarket approval	0910-0231
814, subpart H	Humanitarian Device Exemption	0910-0332
"De Novo Classification Process (Evaluation of Automatic Class III Designation)"	De Novo classification process	0910-0844
"Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff"	Q-submissions	0910-0756
801 and 809	Medical Device Labeling Regulations	0910-0485
822	Postmarket Surveillance of Medical Devices	0910-0449

Dated: August 27, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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